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On 28 Feb 2007

TOWNSEND and TOWNSEND and CREW LLP

By: Malinda Adafit

PATENT
Attorney Docket No.: 02307O-067720US
Client Ref. No.: 96-215-3

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:	Confirmation No. 5513
LALEH SHAYESTEH et al.	Examiner: Jehanne Souaya Sitton
Application No.: 08/905,508	Technology Center/Art Unit: 1634
Filed: August 4, 1997	DECLARATION UNDER 37 CFR 1.132
For: GENETIC ALTERATIONS ASSOCIATED WITH CANCER	
Customer No.: 20350	

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

1. I, Joe W. Gray, am Director, Division of Life Sciences, Lawrence Berkeley National Laboratory and an Adjunct Professor of Laboratory Medicine at the University of California San Francisco. I am a co-inventor of the subject matter disclosed and claimed in the above-referenced patent application.

2. I received a Ph.D. in Physics in 1972 from Kansas State University. My field of expertise is cancer, molecule cytogenetics, and genomics. I have been in this field for over 30 years and have authored over 300 publications in this area.

3. I have read and am familiar with the contents of the above-referenced patent application and claimed subject matter. I understand that the Examiner has rejected the current claims as allegedly unpatentable over the combination of the prior art teachings of Bonjouklian, *et al.* (U.S. Patent No. 5,378,725, "Bonjouklian") in view of Arnold, *et al.* (*Genes,*

Chromosomes, and Cancer 16:46-54, 1996, "Arnold") and Volinia, *et al.* (*Genomics* 24:472-477, 1994, "Volinia") and further in view of Xiao, *et al.* (*International Journal of Oncology* 6:405-411, 1995, "Xiao") or alternatively, Skorski, *et al.* (*Blood* 86:726-736, 1995, "Skorski"). In particular, it is my understanding that the rejection is based on the following arguments.

4. Bonjouklian is characterized by the Examiner as describing administration of a phosphatidyl inositol 3 (PI3) kinase inhibitor, *e.g.*, wortmannin, to treat a PI3 kinase-dependent condition such as abnormal cell growth in a neoplasm such as ovarian cancer. Arnold is described in the rejection as teaching an increase in copy number of 3q26-qter in ovarian tumors. The Examiner alleges that it would have been obvious to one of ordinary skill in the art at the time of the invention to detect amplification of the gene encoding the catalytic subunit of PI3 kinase, *i.e.*, *PIK3CA*, in ovarian cancer cells in a patient and to administer the PI3 kinase inhibitor wortmannin. Specifically, the Examiner contends that it would have been obvious because Arnold teaches that 3q26-qter is amplified in 42% of ovarian tumors that they analyzed and the *PIK3CA* gene is found at 3q26.3 (as taught by Volinia); and Bonjouklian teaches administration of a PI3 kinase inhibitor. The Examiner cites Xiao and Skorski as teaching that wortmannin inhibits proliferation of gastric cancer cell lines that overexpress PI3 kinase and of leukemia cells that require PI3 kinase for proliferation. It is the Examiner's position that Xiao and Skorski provide a basis for expecting that wortmannin treatment of ovarian cancer cells, as allegedly suggested by Bonjouklian, would inhibit proliferation.

5. This declaration is provided to show that the fact that the broad region of 3q26-qter was known to be amplified in ovarian cancer would not lead one of skill in the art to conclude that amplification of *PIK3CA*, which is one of numerous genes located in this broad region, leads to overexpression of PIK3CA and is therefore indicative of a role for PI3 kinase in oncogenesis in ovarian cancer cells that contain the amplified region.

6. Arnold describes a comparative genomic hybridization (CGH) study of forty nine ovarian cancer tumors. In this CGH analysis, differentially labelled total genomic DNA from a tumor sample and from a normal reference control sample were co-hybridized to normal metaphase chromosomes. The resulting ratio of the fluorescence intensities of the probes hybridized to the chromosomes is approximately proportional to the ratio of the copy numbers of

the corresponding DNA sequences in the tumor and normal reference genomes. Arnold identified the region of 3q26-qter as being increased in copy number in 42% of the ovarian tumors that were analyzed. However, although it was known in the art that the gene encoding the catalytic subunit of PI3 kinase (PIK3CA) is located at 3q26.3, the CGH study as performed by Arnold using metaphase chromosomes does not provide sufficient resolution to determine that the chromosomal subregion containing the PIK3CA locus is a focal point of amplification.

7. Furthermore, even though a gene may be present in an amplified chromosomal region, that fact alone does not lead one of skill to conclude that a particular gene is overexpressed. Many genes are present in chromosomal region 3q26-qter. For example the genome browser of the University of California, Santa Cruz (http://genome.ucsc.edu/cgi-bin/hgTracks?hgsid=83748260&clade=vertebrate&org=Human&db=hg18&position=3q26&pix=620&Submit=submit&hgsid=83748260, a print out of which is attached hereto, shows that numerous genes are located in the 3q26 region alone; however, there is no evidence that all or most of the products of these many genes are overexpressed in ovarian tumors.

8. It is my opinion as one who has practiced in this art for many years that although *PIK3CA* may have been identified as a potential gene of interest in the 3q26-qter region identified by Arnold due to its biological function in proliferation or its overexpression in other cancers, at the time of the invention one of skill could not have concluded that the mere presence of the gene in this broadly amplified region would predictably lead to a correlation with overexpression of the protein and an oncogenic role in ovarian cancer cell proliferation.

9. I further declare that all statements made herein of my knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both (18 U.S.C. § 1001), and may jeopardize the validity of the patent application or any patent issuing thereon.

Dated: 2/26/07

Joe Gray, Ph.D.